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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,739	12/24/2003	Nabil Hanna	037003-0307368	9111

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
11/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/743,739	HANNA ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,51-65 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47,51-65 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/10/07 has been entered.

Accordingly, claims 47, 51-65, 68 are being examined.

Withdrawn Rejection

The 112, first paragraph, new matter of claim 64 has been withdrawn in view of the amendment.

Obviousness-type Double Patenting

Claims 47, 51-65, 68 of the instant application remain non-provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-2, 4-19 of US Application Serial No. 09/853581, now US patent No. 6,998,125, for reasons already of record in paper of 01/22/07.

The response asserts that a terminal disclaimer executed by the undersigned will be considered when one or more claims of the instant application are in condition for allowance.

The rejection remains, for reasons already of record in paper of 01/22/07. The issue of execution of a terminal disclaimer however will be delayed until the time of allowance, if the examined claims were allowable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 47, 51-63, 65, 68 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Raychaudhuri et al (US 5,695,770, filed on 06/07/1995), in view of Woodworth C D et al, June 1996 (Cell Growth & Differentiation, 7: 811-820), and Segarini et al (WO 94/09815, of record), and as evidenced by Schmolka et al, 1977 (J Am Oil Chem Soc, 54: 110-116, IDS #JJR submitted on 12/12/05), for reasons already of record in paper of 01/22/07.

It is noted claim 47 is rejected only to the extent of a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response, wherein the TGF-beta antagonist is **anti-TGF-beta antibodies**.

The response asserts that the complete text of Ozbun et al. (1996) J. Virol. 70(8):5437-5446 is submitted with the instant response. The response asserts that as one example of reports of TGF beta activity that are contrary to that of Woodworth, this reference shows that TGFI~ induces HPV-positive keratinocytes and cervical cancer cells to differentiate in a tissue culture

system that models conditions in vivo. The response asserts that specifically, Ozbun describes that the authors have "employed an organotypic tissue culture system which emulates the three-dimensional architecture and differentiation scheme of keratinocytes in vivo" (page 5438, column 1). The response concludes that thus, contrary to the assertion of the examiner, the results of Ozbun were obtained under conditions that support differentiation. The response asserts that as asserted previously, these results are directly opposite to those of Woodworth. In view of such conflicting results, i.e., that TGF-beta can either promote or inhibit proliferation of HPV-positive keratinocytes, and specifically that TGF-beta inhibits proliferation of cervical cancer cells, one of skill in the art would not readily conclude that the presently claimed combination method could be performed with a reasonable chance of success.

The response has been considered but is not found to be persuasive for the following reasons:

The full reference by Ozbun has not been received by the Office, and therefore the response arguments cannot be assessed.

The response asserts that the results are unexpected, and that one could not have reasonably predicted that the combined use of an antigen formulation and an agent that inhibits TGF[3 activation would elicit synergistic CTL-inducing responses as described in the instant application. The response asserts that in particular, Figures 2A-2B demonstrate the anti-tumor activity of E7-PROVAX® when used in combination with an inhibitory anti-TGFI3 antibody. The response assdrts that figure 2A shows that administration of E7-PROVAX® had no effect on tumor growth, i.e., the response closely tracked that of tumor-bearing animals that received no

treatment (control). The response assert that likewise, administration of an inhibitory anti-TGFI3 antibody showed a minimal anti-tumor response that also closely tracked the control. The response asserts that by contrast, animals receiving both agents showed marked inhibition of tumor growth. The response concludes that thus, a previously inactive single agent, E7-PROVAX®, was rendered effective by use in combination with a second agent, an anti-TGFI3 antibody. The response asserts that the outcome of the combined treatment is synergistic or greater than additive, i.e., more than the sum of zero effect (the effect of E7-PROVAX® as a single agent) plus the effect of the inhibitory anti-TGFI3 antibody. The response asserts that figure 2B shows similar results. The response asserts that the effect of repeated administration of an anti-TGFI3 antibody increases its anti-tumor response, however, the combined effect of E7-PROVAX® plus anti-TGFI3 antibody is still synergistic or greater than additive.

The response has been considered but is not found to be persuasive for the following reasons:

The response argues limitation not in the claims, which do not recite synergistic effect. Further, the claims are only drawn to a method for enhancing an antigen-specific CTL response against cervical cancer cells, which is not necessarily reducing cancer growth, and which CTL response certainly is not an unexpected result. One would have a reasonable expectation of success when combine HPV 16 E7 antigen taught by Raychaudhuri et al with an inhibitor of TGF-beta taught by WO 94/09815, for use in the method of enhancing CTL response in cancer cells, such as cervical cancer, taught by Raychaudhuri et al, because TGF-beta enhances growth of HPV-immortalized cells under conditions that induce squamous differentiation, which conditions resemble cervical dysplasia, and providing a relevant to model for malignant

transformation, as taught by Woodworth et al, and because an inhibitor of TGF-beta is expected to suppress in the activity of TGF-beta, including the activity of enhancing growth of HPV-immortalized cells.

B. Claims 47, 51-63, 65, 68 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Raychaudhuri et al (US 5,695,770, filed on 06/07/1995), in view of Woodworth C D et al, June 1996 (Cell Growth & Differentiation, 7: 811-820), and Segarini et al (WO 94/09815, of record), and as evidenced by Schmolka et al, 1977 (J Am Oil Chem Soc, 54: 110-116, IDS #JJR submitted on 12/12/05), and further in view of Schultz-Cherry et al, 1995 (JBC, 270 (13): 7304-7310) or Capon DJ et al (WO 91/08298).

It is noted that the dependent claims 51-63, 65, 68 clearly belong to this rejection, but were inadvertently not recited in the previous Office action.

In this rejection, claim 47 is rejected to the extent of a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response, wherein **the TGF-beta antagonist is a TGF-beta receptor linked to a constant region of an immunoglobulin or the thrombospondin peptide GGWSHW.**

The response asserts that the combined teachings of Raychaudhuri, Woodworth, Segarini, and Schmolka do not establish a prima facie case of obviousness, because Raychaudhuri et al. does not describe or suggest the presently claimed method, and the cited secondary references would not have provided suggestion or motivation to one of ordinary skill in the art to modify the method of Raychaudhuri et al. to obtain the claimed invention with a reasonable expectation

of success. The response asserts that in addition, the synergistic effects of the claimed combination are unexpected and further support the non-obviousness of the invention.

The response has been considered but is not found to be persuasive for the following reasons:

The claimed invention is clearly obvious over the teaching of Raychaudhuri et al (US 5,695,770), Woodworth et al, WO 94/09815, and Schmolka et al , supra.

Further, it would have been obvious to replace the anti-TFG-beta antibodies in the method taught by Raychaudhuri et al (US 5,695,770), Woodworth et al, WO 94/09815, and Schmolka with another TGF-beta antagonist, such as the thrombospondin peptide GGWSHW taught by Schultz-Cherry et al or a TGF-beta receptor linked to a constant region of an immunoglobulin, taught by WO 91/08298, because using the thrombospondin peptide GGWSHW or the TGF-beta receptor linked to a constant region of an immunoglobulin provides alternative treatment methods, and thus increasing the versatility of the treatment methods.

NEW REJECTION BASED ON THE AMENDMENT

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 64 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "low levels of an immunostimulating peptide" in claim 64 is a relative term which renders the claim indefinite. The term " low levels of an immunostimulating peptide " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Further, it is not clear which immunostimulating peptide is referred to, because there are numerous immunostimulating peptides, and because it is not clear which of these peptides could diminish a cellular response, which cellular response could be any response, and not necessarily an immune response.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
October 19, 2007

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